

### **REMARKS**

#### **Status of the Claims**

Claims 2, 7, 8, and 17-19 are currently pending. Claim 2 has been amended to clarify the invention. No new matter has been added. Upon entry of the amendments, claims 2, 7, 8, and 17-19 will be pending. Entry of the amendments and reconsideration in view of the following comments are respectfully requested.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

#### **Objection to the Claims**

Claim 2 is objected due to a lack of clarity, specifically because the acronyms “*ccr*” and “*icm*” are not spelled out. The Office further suggests amending the language of claim 2 to recite “a recombinant gene encoding crotonyl CoA reductase (*ccr*) selected from the group consisting of, a *ccr* from *Streptomyces cinnamonensis* and *Streptomyces collinus*; and an *icm* from *Streptomyces cinnamonensis*”. The language of claim 2 has been amended to address the Office’s concerns regarding clarity. Accordingly, this objection may properly be withdrawn.

#### **Rejection under 35 U.S.C. § 103(a)**

Claims 2, 7-8 and 17-19 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Katz, *et al.* (US 6,004,787, issued Dec. 21, 1999, hereinafter “Katz”) in view of Stassi, *et al.* (*Proc. Natl. Acad. Sci. USA* 1998, 95:7305-7309, hereinafter “Stassi”).

The Office asserts that Katz teaches the use of vectors and host cells in a method to produce novel polyketide structures by designing and introducing specified changes in the DNA governing

the synthesis of the polyketide accomplished by introducing one or more specified changes into the DNA sequence, such as substituting modules. The Office acknowledges that Katz is silent on an acyl transferase (AT) domain specific for ethylmalonyl CoA. To cure this deficiency of Katz, the Office cites Stassi, which allegedly teaches ethyl-substituted erythromycin and two or more extender modules with AT domain specificity. The Office further asserts that Stassi discloses the construction of hybrid PKSs through replacement of AT domains with those that specify different starter or extender units. Accordingly, the Office concludes that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention because Katz indicates that PKS modules can be substituted for each other and Stassi demonstrates the replacement of methyl for ethyl. The Office asserts that results of such substitution would have been predictable, and therefore the claimed invention is *prima facie* obvious.

Applicants respectfully traverse this rejection for the reasons set forth below.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). To establish a *prima facie* case of obviousness a three-prong test must be met. First, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference to achieve the claimed invention. *KSR* at 1731. And third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). Rejections on obviousness grounds

cannot be sustained by mere conclusory statements. *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2007) (citations omitted). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Evidence of an unobvious or unexpected advantageous property can rebut *prima facie* obviousness. MPEP § 716.02(a). Moreover, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP § 2143.01.VI.

Claim 1 of the present invention (and all the claims dependent therefrom) includes the following limitation: a recombinant polyketide synthase gene that encodes a loading module comprising an inactivated beta-ketoacyl synthase (KS<sup>Q</sup>) domain, an acyl transferase (AT) domain specific for ethylmalonyl CoA, and an acyl carrier protein (ACP) domain (emphasis added). Katz teaches the general notion that novel polyketide structures may be produced by substituting different PKS modules for one another. At the Office correctly noted, Katz does not teach an acyl transferase (AT) domain specific for ethylmalonyl CoA. As mentioned above, the Office cited Stassi to cure that deficiency. However, a careful reading of Stassi reveals a number of significant problems.

As an initial matter, neither Katz nor Stassi teaches a loading module comprising a KS<sup>Q</sup> domain. The present specification explains the function of the KS<sup>Q</sup> domain at page 14, lines 18-22:

The host cells of the invention are particularly suited for expressing such hybrid PKS genes, because the host cells make butyryl CoA, which is converted to ethylmalonyl CoA. The loading module AT domain binds the ethylmalonyl CoA produced, and the KS<sup>Q</sup> domain decarboxylates the ethylmalonyl CoA during its incorporation into the polyketide. (Emphasis added)

Moreover, neither Katz nor Stassi teaches a loading module (i.e., starter unit) comprising an ethylmalonyl CoA-specific AT domain. Stassi teaches that although “in *S. erythraea* expressing the *S. collinus ccr* gene, replacements in [extender] modules 1 through 4 with the ethylmalonate-specific AT produced compounds with electrospray ionization mass spectra consistent with

production of ethyl substitutions for methyl groups at C-12, C-10, C-8, and C-6, respectively,” “those in [extender] modules 5 and 6 did not produce compounds of mass 748” (page 7309, left column, last paragraph; emphasis added). Stassi further teaches that “even though genetic information may be present for the production of novel compounds, it is still not possible to predict which substitutions will yield detectable levels of product” (page 7309, right column, first paragraph; emphasis added). Thus, not only does Stassi not teach a loading module comprising an ethylmalonyl CoA-specific AT domain, it expressly states that it is impossible to determine *a priori* which domain substitutions will be successful. Thus, the Office’s statement that “results would have been predictable” (the OA at page 4) is contradicted by the very reference used to build a case for *prima facie* obviousness.

Although the Supreme Court’s *KSR* decision made it easier for the Patent Office to combine multiple reference in order to establish *prima facie* obviousness, it also endorsed the longstanding proposition that “when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious” (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). In this case, not only does the combination of Katz and Stassi fail to teach each and every element of the present invention, the prior art actually teaches away from combining these references. A person of ordinary skill in the art at the time of the invention would not have been motivated to introduce a KS<sup>Q</sup> domain and an ethylmalonyl CoA-specific AT domain into a PKS loading module with a reasonable expectation of success because Stassi expressly teaches that “it is still not possible to predict which substitutions will yield detectable levels of product”. Accordingly, Applicants respectfully submit that the Office failed to establish a *prima facie* case of obviousness, and therefore this rejection may properly be withdrawn.

**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. **300622004810**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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